

The Addition of Morpholine To  
Unsaturated Esters

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BOSTON UNIVERSITY

GRADUATE SCHOOL

Thesis

THE ADDITION OF MORPHOLINE TO UNSATURATED ESTERS

by

Roy Laible

(B.S., Northeastern University, 1945)

submitted in partial fulfillment of the

requirements for the degree of

Master of Arts

1948





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### Introduction

Morpholine,  $\text{O} \begin{pmatrix} \text{CH}_2 - \text{CH}_2 \\ | \quad | \\ \text{CH}_2 - \text{CH}_2 \end{pmatrix} \text{H}$ , is a cyclic secondary amine which Gardner and Clarke added to compounds containing  $\alpha, \beta$  - unsaturated linkages such as the ethyl ester and the acid chloride of cinnamic acid. From these reactions they prepared compounds which had considerable anesthetic activity and low toxicity (1). This work prompted Mario Giella to investigate the reaction of morpholine with methyl acrylate at Boston University in 1939 (2). He successfully added morpholine to methyl acrylate by 1,4-addition and prepared various derivatives of the product obtained. It is proposed to repeat portions of Giella's work and to extend this work to include the addition of morpholine to ethyl acrylate and methyl methacrylate. Particular attention will be paid to the red crystals which formed as a by-product when Giella added morpholine to methyl acrylate.

The addition of morpholine to methyl methacrylate, especially, was expected to prove interesting. Jacobson found that irradiation was needed to add thiophenol to methyl methacrylate(3). Gershbein and Hurd found that hydrogen sulfide will add to methyl acrylate, acrylonitrile, or crotonaldehyde when a basic catalyst is present but not to methyl methacrylate(4). The catalyst used was a "Triton B" solution put out by Röhm and Haas. Other workers have used mercuric salts or long periods of reaction to successfully add thiols to methyl methacrylate. From these



results it is expected that morpholine will probably add with difficulty or not at all to methyl methacrylate.

Ethyl acrylate was chosen as the other unsaturated ester because the type of compound formed might have useful anesthetic properties. The grouping  $\text{>N-C-C-C-O}$  seems to be responsible for the physiological action of alkaloids. The addition products of morpholine with all three esters mentioned would contain this grouping. However, the product formed from either of the methyl esters would have the disadvantage of hydrolyzing to give poisonous methyl alcohol. If the addition product of morpholine and ethyl acrylate hydrolyzed non-toxic ethyl alcohol would be given off.



### Further Investigation Of The Red Crystals Formed When Morpholine Is Added To Unsaturated Esters

Giella found that when morpholine was added to methyl acrylate containing hydroquinone red crystals formed, the melting point of which tallied with the product formed when morpholine was added to an ether solution of hydroquinone. A British patent gives procedures for producing red-purple wool dyes by condensing halogenated anthraquinones with morpholine (5). By analogy it was thought that the red crystals Giella found might be of some value as a dye. In order to determine the nature of these crystals, further experiments and analyses were deemed necessary. Some of these experiments were carried out in an inert atmosphere of nitrogen in order to observe the effect of oxygen on the formation of the red crystals.

When a solution of benzoquinone in ethyl acetate was placed in an inert atmosphere of nitrogen, and morpholine added through a separatory funnel, the red crystals formed immediately. These crystals were filtered and washed with ether. The melting point was  $233^{\circ}\text{C}$ . In order to see if the red color was inherent in these crystals, they were recrystallized from glacial acetic acid and sodium dichromate. The melting point became  $234^{\circ}\text{C}$  but the red color was still present. When glacial acetic acid and Norite decolorizing charcoal were used as recrystallizing agents the melting point was raised to  $235^{\circ}\text{C}$ .





A mixed melting point of the red crystals formed in the reaction of morpholine and unsaturated esters containing hydroquinone with those prepared as above melted at  $235^{\circ}\text{C}$  with no depression. Both sets of crystals were recrystallized from glacial acetic acid and Norite charcoal.

When a solution of hydroquinone in ethyl acetate was placed in an atmosphere of nitrogen and morpholine added through a separatory funnel no red solution or red crystals appeared. As soon as air was allowed to enter, the solution became red and the red crystals appeared shortly after. Thus

it would seem that air oxidation is necessary for morpholine and hydroquinone to react. These crystals did not depress the melting point of the crystals formed when morpholine is added to esters containing hydroquinone.

Elementary analysis for carbon, hydrogen, and nitrogen gave the following average results for the crystals formed from the reaction between morpholine and hydroquinone.

C	H	N
61.40%	7.09%	9.30%

One analysis was run on the red crystals formed in the reaction of morpholine with methyl acrylate containing hydroquinone.

C	H	N
61.58%	7.448%	9.48%

This seems to be additional proof that the red crystals formed when morpholine is added to unsaturated esters is due to the reaction between morpholine and the hydroquinone used.

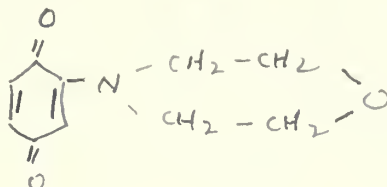


as a stabilizer and not between the amino ester formed during the reaction and the hydroquinone. This latter possibility existed because Fischer and Schrader found that amino esters react with benzoquinone (6).

Suida and Suids found that primary and secondary amines add to benzoquinone. Further, they say a monoanilide should predominate if the reaction is carried out in dilute acetic acid solution and a dianilide should predominate in an alcoholic solution (7). To check this possibility the reaction of morpholine with hydroquinone was carried out once in alcoholic solution and once in a dilute acetic acid solution. The melting point obtained in each case was identical.

The theoretical carbon, hydrogen, and nitrogen analyses for some different possibilities are given here.

1.  $C_{10}H_{11}O_3N$  - Molecular Weight - 193.1

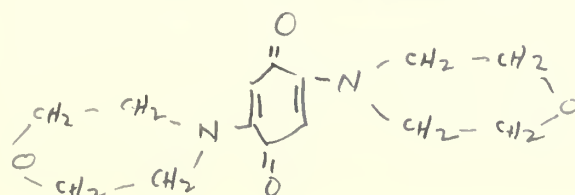


C  
62.15%

H  
5.74%

N  
7.25%

2.  $C_{14}H_{18}O_2N_2$  - Molecular Weight - 278.1



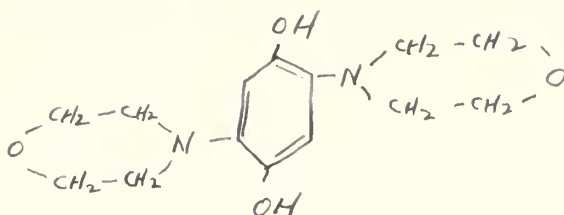
C  
60.41%

H  
6.52%

N  
10.07%



3.  $C_{14}H_{20}O_4N_2$  - Molecular Weight - 280.1



C  
60.01%

H  
7.20%

N  
9.99%

The red crystals found seem to check most nearly with the second possibility. Amolecular weight determination would narrow down the possibilities, but no suitable solvent for a molecular weight determination has been found.

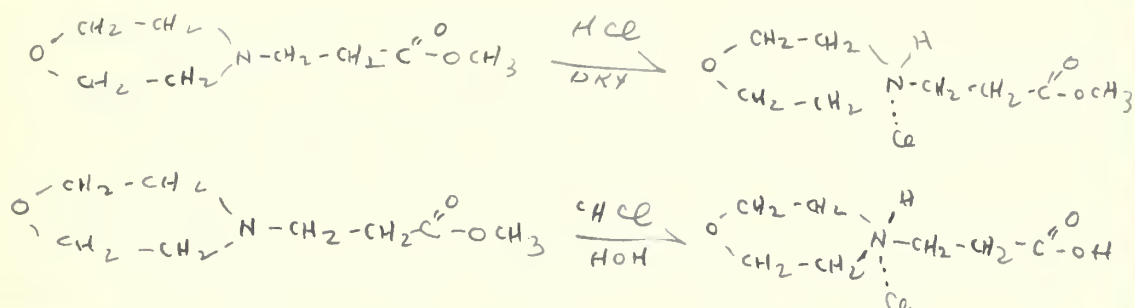
A piece of cotton cloth was treated with a solution of the red crystals in dilute acetic acid and then allowed to dry. The red color was found to wash out with plain water. From this experiment it is seen that these red crystals would not be a good dye for cotton. It is suggested that similar experiments be carried out with animal fibers.





Mixed Melting Point Of Methyl  $\beta$ -4 - Morpholine  
 Propionate Hydrochloride and  
 $\beta$ -4 - Morpholine Propionic Acid Hydrochloride

Reactions:



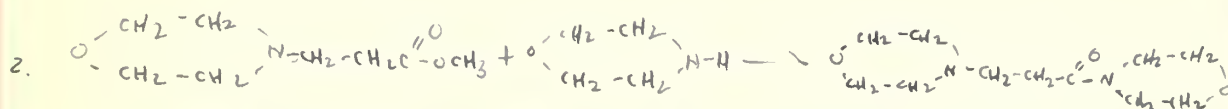
Giella prepared both the ester hydrochloride and the acid hydrochloride from methyl  $\beta$ -4 - morpholine propionate. To make sure the two were not identical it was decided to prepare them both and run a mixed melting point.

The ester hydrochloride is prepared by passing dry HCl through a solution of the ester in ether while the acid hydrochloride is obtained by heating a solution of the ester in concentrated hydrochloric acid on a steam bath. The former melts at 204°C while the latter melts at 212°C. The melting point of a mixture of the two compounds is depressed to 190°C. A molecular weight determination was run on the ester hydrochloride by titrating with NaOH to the phenolphthalein endpoint. A value of 206 was obtained which is 1.7% less than the theoretical value of 209.5.



## N(β-4 - Morpholine Propionyl) Morpholine

## Reaction



Giella found that when two equivalents of morpholine were allowed to stand with one equivalent of methyl acrylate for a period of four months white crystals formed. He proved this compound to be the substituted amide by analysis.

In order to compare the yields of the substituted amide by different procedures the following experiments were carried out:

- a. Two equivalents of morpholine were allowed to stand for six weeks with one equivalent of methyl acrylate. At the end of that period no crystals had appeared so the mixture was distilled under reduced pressure. No yield was obtained. Apparently the reaction time needed is more than six weeks.
- b. Two equivalents of morpholine were refluxed with one equivalent of methyl acrylate for two hours. The mixture was then distilled under reduced pressure. No yield of the amide was obtained.
- c. The ester formed by 1, 4-addition was refluxed with excess morpholine for two hours. Then the morpholine and ester which had not reacted were distilled off. The residue left in the flask solidified on cooling. This residue was extracted with



ether by a Soxhlet extractor and a 55% yield of the amide was obtained. The picrate of the amide was made. It melted at 129°C as Giella found.



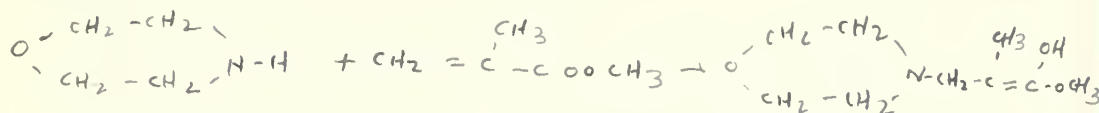
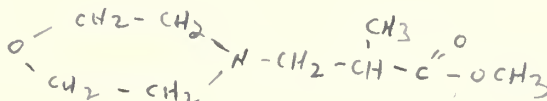


## Addition of Morpholine To Methyl Methacrylate

To Form Methyl 3-4 - Morpholine

Methyl Propionate

## Reaction

Rearrangement

## Procedure

1. 43.5cc (1/2 mole) of morpholine was added to 53.5cc (1/2 mole) of methyl methacrylate in a round bottomed flask to which was attached a reflux condensor. The evolved heat expected from the reaction by analogy to the addition of morpholine to methyl acrylate was not evident. The mixture was then refluxed for 45 minutes and the mixture distilled under reduced pressure. No yield was obtained.
2. More reaction mixtures of morpholine and methyl methacrylate were allowed to stand various periods of time. The optimum time seemed to be about 3 weeks. 50 grams of liquid boiling at 124°C under a reduced pressure of 20mm was obtained. This was 53% yield. The refractive index was 1.4520 and checked on different samples.



## Analyses

Elementary analyses on  $C_9H_{17}O_3N$  gave the following results:

	C	H	N
Found	57.12%	9.30%	7.26%
Theoretical	57.72%	9.16%	7.48%

Although these values are in good agreement, it must be pointed out that the precision between different runs is not good. This may be due to the difficulty in purifying a liquid. A molecular weight determination by saponification was attempted on the ester. Phenolphthalein did not give a sharp enough endpoint for this molecular weight determination to be acceptable. A molecular weight of 226 was found on the ester hydrochloride. This value agrees well with the theoretical value of 223.6 .

## Discussion of Results

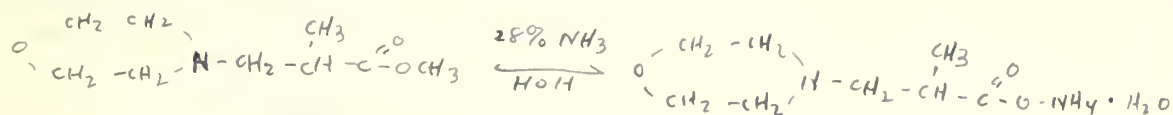
From the analyses found on the ester and the molecular weight determination on the ester hydrochloride, it would seem that morpholine can be added to methyl methacrylate. However, the yield obtained is 53% in three weeks as contrasted with the 88% yield obtained in one day when morpholine is added to methyl acrylate. In addition, there is no noticeable evolution of heat when morpholine and methyl methacrylate are mixed while the extremely exothermic reaction of morpholine and methyl acrylate requires cooling to prevent evaporation of the liquid mixture (2).



# The Reaction Between Methyl $\beta$ -4 - Morpholine

## $\alpha$ - Methyl Propionate And Ammonia

### Reaction



### Procedure

20 grams of methyl  $\beta$ -4 - morpholine  $\alpha$ -methyl propionate and 100cc of 28% ammonia were allowed to stand in a 200cc stoppered flask for nine days. At the end of this time the flask was allowed to stand open for a day and then slowly evaporated down to 30cc on a steam bath. The solution must be allowed to stand for some time before crystals form. Ten grams of crystals were obtained which melted at 56-58°C after being recrystallized from ethyl acetate. The crystals seemed dry and pure but on being dried in a desiccator containing calcium chloride gave off a liquid which was not absorbed very strongly. Drying in a desiccator containing phosphorous pentoxide produced the same results.

### Analysis

As this compound decomposed when placed in a desiccator, it could only be air-dried before analysis. The average results obtained are as follows:

C	H	N
51.07%	9.51%	10.07%





These results correspond most closely to the ammonium salt containing one mole of water of crystallization. The theoretical values for this possibility are:

C	H	N
51.92%	9.64%	13.5%

The low nitrogen value obtained could be explained by a non-nitrogen containing impurity. If ammonia were evolved from the ammonium salt, the corresponding acid would be left. If this acid contained two moles of water in its hydrated form, it would contribute the following analyses.

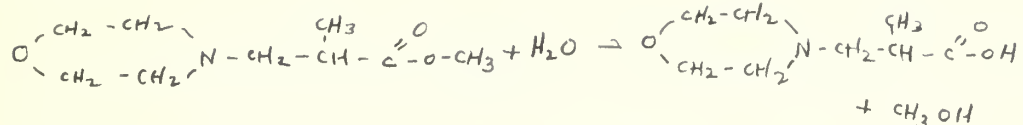
C	H	N
51.8%	9.85%	5.62%

This hydrated acid as an impurity would account for the low nitrogen values obtained and the good agreement of the carbon and hydrogen values. Giella found that the analogous ammonium salt gave off ammonia on dry distillation, leaving the acid behind. He also found evidence to support the fact the analogous acid exists in the di-H<sub>2</sub>O form unless dried in a desiccator.



*β*-4- Morpholino Isobutyric Acid

## Reaction



## Discussion

Giella's method for preparing *β*-4- morpholino propionic acid was used in the hope that the homolog with the *α*- methyl group would undergo the same hydrolysis(2). A base is not used to catalyze this hydrolysis because of the extreme solubility of amino acids in water. This solubility in water and insolubility in ether would make it difficult to separate the acid formed from the inorganic salt resulting from the neutralization of the acid.

## Procedure

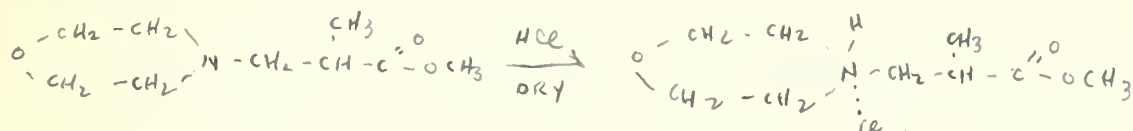
1/20 of a mole of the ester was dissolved in 40cc. of water in a 250cc round-bottomed flask to which was attached a fractionating column fitted with a downward water condenser. The mixture was refluxed for two hours during which time a distillate was collected which gave a test for alcohol with ceric nitrate. The mixture had become dark brown and after extracting with ether and concentrating on a water bath had the consistency of molasses. It appears that the ester decomposes as it is hydrolyzing.



## Preparation Of The Hydrochloride Of Methyl

 $\beta$ -4 - Morpholine  $\alpha$ -Methyl Propionate

## Reaction



## Discussion

The hydrochloride of methyl  $\beta$ -4 - morpholine  $\alpha$ -methyl propionate was prepared for the following two reasons:

1. To carry out a molecular weight determination.
2. To compare it to methyl  $\beta$ -4 - morpholine propionate hydrochloride.

## Procedure

The hydrochloride was prepared by passing dry HCl through a solution of the ester in ether. The melting point of the crystals so obtained was  $174^\circ\text{C}$  when recrystallized from absolute alcohol. This melting point is 30 degrees lower than that obtained with methyl  $\beta$ -4 - morpholine propionate hydrochloride. This drop in melting point is expected since methyl  $\beta$ -4 - morpholine  $\alpha$ -methyl propionate contains an extra methylene group. This increase in total molecular weight decreased the fraction of the molecule which is polar. The molecular weight was determined by titrating the ester hydrochloride with NaOH to a phenolphthalein end point. The molecular weight found was 226 which closely approximates the calculated value of 223.6.









Ethyl  $\beta$ -4 - Morpholine Propionate Hydrochloride

## Reaction



The hydrochloride of ethyl  $\beta$ -4 - morpholine propionate hydrochloride is prepared by passing dry HCl through a solution of the ester in ether. The product was obtained in 90% yield and melted at  $177^\circ\text{C}$  when recrystallized from ethyl alcohol. The molecular weight was determined by titrating a sample of hydrochloride with  $\text{NaOH}$  to the phenolphthalein end point. A value of 224.7 was found as compared to the theoretical value of 223.6. Elementary analysis gave the following results:

Found	C	H	N
	48.42%	7.85%	6.14%

Theoretical for  $\text{C}_9\text{H}_{18}\text{O}_3\text{NCl}$

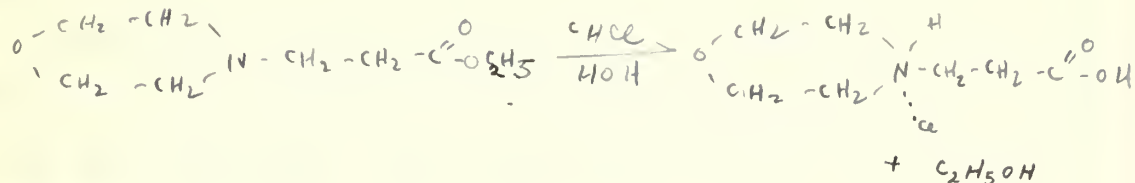
	C	H	N
	48.40%	8.07%	6.25%



# $\beta$ -4 - morpholine Propionic Acid Hydrochloride

From Ethyl  $\beta$ -4 - Morpholine Propionate

## Reaction



## Discussion

It was decided to try to prepare the acid hydrochloride from the ethyl ester. As Mario Giella prepared it from methyl  $\beta$ -4 - morpholine propionate, a mixed melting point of the two products would show if the same compound was obtained in each case.

## Preparation

One gram of the ester was heated on a steam bath with 10cc of concentrated hydrochloric acid. As the mixture evaporated white crystals appeared. These crystals melted at  $212^\circ\text{C}$  and did not depress the melting point of the compound prepared by Giella from the methyl ester.



### Digest Of Thesis

It has been found that morpholine will add to ethyl acrylate with a vigorous evolution of heat as Giella found to be the case when he added morpholine to methyl acrylate. The amount of heat evolved and the yield obtained are very similar in the two reactions. Both reactions probably go by 1, 4-addition.

The addition of morpholine to methyl methacrylate is quite different however. The three main differences are as follows:

1. No evolved heat is noticed.
2. A much longer period of reaction is necessary to yield a product.
3. A much smaller yield was obtained.

Except for the hydrochloride of the ester the derivatives of the product of morpholine and methyl methacrylate are obtained in poor yield or are unstable. The product formed from methyl  $\beta$ -4 - morpholine  $\alpha$ -methyl propionate and ammonia decomposes in a desiccator. Although water hydrolysis of this product of morpholine and methyl methacrylate can be accomplished, decomposition takes place and the only product obtained is a molasses-like liquid. Acid hydrolysis of the product of morpholine and methyl methacrylate (methyl  $\beta$ -4 - morpholine  $\alpha$ -methyl propionate) yields the amino acid hydrochloride in very small amounts. This is contrasted with the almost quantitative yields of the amino acid hydrochloride obtained from the acid hydrolysis of either the ester formed from



morpholine and methyl acrylate or (methyl 4 - morpholine propionate) or that formed from morpholine and ethyl acrylate (ethyl 4 - morpholine propionate).

The following new compounds have been prepared:

1. Methyl  $\beta$ -4 - morpholine  $\alpha$ -methyl propionate.
2. Methyl  $\beta$ -4 - morpholine  $\alpha$ -methyl propionate hydrochloride.
3. Ethyl  $\beta$ -4 - morpholine propionate.
4. Ethyl  $\beta$ -4 - morpholine propionate hydrochloride.
5. Ammonium  $\beta$ -4 - morpholine  $\alpha$ -methyl propionate.

The red crystals first found by Giella were analyzed and proved more conclusively to be due to the reaction of morpholine with hydroquinone.





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